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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/465,747	06/06/95	BROWN C	DARU-2/CONT

18M1/0219

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EXAMINER	
MOSHER,M	
ART UNIT	**PAPER NUMBER**
1815	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/465,747	Applicant(s) Brown
	Examiner Mary E. Mosher	Group Art Unit 1815

☒ Responsive to communication(s) filed on *6/6/95, 9/29/95, 2/26/96, 5/15/96*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *49-57* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *51 and 52* is/are allowed.

☒ Claim(s) *49, 50, and 53-57* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *20, 23*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1815.

Allowable Subject Matter

Claims 51 and 52 are allowable. Carter et al (newly cited) provides evidence that one skilled in the art would have expected VP1 to be required for assembly of virus-like particles.

Claim Rejections - 35 USC § 112

Claim 54 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for virus-like particles comprising VP1 and VP2, does not reasonably provide enablement for virus-like particles comprising VP1 in the absence of VP2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Young et al (5,508,186) is cited as evidence that VP1 fails to form a virus-like particle in the absence of VP2. See column 11 line 50 to column 12 line 23. Therefore the teachings of the instant specification are seen as inadequate to enable the full scope of the claim, which encompasses particles consisting of VP1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 49 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Ozawa et al (Journal of Biological Chemistry 263:10922-10926, 1988). Ozawa et al teaches B19 capsid proteins VP1 and VP2 which were isolated by synthesis using in vitro translation from an isolated synthetic mRNA, and purified by immunoprecipitation. See page 10923, second column, under "In vitro production of capsid proteins by synthetic B19 transcripts". These proteins meet each and every limitation of the claims.

Claim Rejections - 35 USC § 103

In making the following rejections, claims 53, 54, and 57 are denied the benefit of the filing date of priority application NL 8902301 because the application does not adequately describe or teach how to make virus-like particles as claimed. The NL application discusses virus-like particles which consist of VP1 and VP2, see for example page 4, lines 18-24 and 30-32. The application also discusses "recombinant virus-like particles which consist of VP1 and/or VP2", see for example page 5, lines 30-32. However the application provides no working examples showing production of virus-like particles. The application identifies a preferred method of making particles which consist of VP1 and VP2, using a vector including splice sites so that both products would be produced from a single coding sequence. However, this method is not described in the PCT application. A different method, involving co-infection with two coding sequences, is used in the PCT application. Therefore it appears that the NL application does not describe an effective method to provide a baculovirus expression system which is necessary for expression of both VP1

and VP2 proteins. In addition, the PCT application makes clear that VP2, but not VP1, is capable of forming a virus-like particle. Since the NL application teaches a different, apparently unsuccessful method for making particles containing VP1+VP2, and since the priority application provides no blazemarks to the subunit which is capable of assembling as a virus-like particle, it appears that the priority application lacks a written description or an enabling disclosure for the virus-like particles. The effective date for claims 53, 54, and 57 is therefore September 11, 1990.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 49, 50, 55, and 56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406), Ozawa et al (1988), Sisk et al, and Cotmore et al in view of any or all of Smith et al, Pennock et al, Luckow et al and Wood et al. As discussed previously, Ozawa et al (J. Virol 61(8):2395-2406) discloses the transcription map of the B19 human parvovirus, including the location of the genes for the 84 Kd VP1 antigen and the 58 Kd VP2 antigen (p. 2403, Fig.9). Cotmore et al also disclose the location of the VP1 and VP2 genes on the human parvovirus B19 genome by shotgun cloning restriction fragments from the cloned viral genome, expressing those fragments in E. coli, and detecting the expressed capsid polypeptides with diagnostic human anti-B19 serum. Sisk et al disclose the expression of a VP1-β galactosidase fusion protein in E. coli that is recognized by anti-B19 serum. Additionally, Sisk

et al disclose the need to produce B19 viral capsid proteins by recombinant means as viral growth in tissue culture does not produce significant quantities of antigen (see Sisk et al, p. 1077, second paragraph). In addition, Ozawa et al (1988) teaches separate nucleic acids encoding VP1 and VP2. None of these references disclose the expression of VP1 or VP2 in recombinant baculovirus infected insect cells. However, Smith et al, Pennock et al, Luckow et al all teach expression of proteins using baculovirus expression vectors, teaching high-level production, safety, and similarity to authentic native proteins; Wood et al further teaches use of baculovirus expression vectors to produce an immunoprotective capsid protein from another parvovirus.

Given the art recognized need for the large scale production of the human parvovirus B19 capsid antigens as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as exemplified by Ozawa et al (J. Virol 61(8):2395-2406), Ozawa et al (1988) and Cotmore et al, as well as the disclosed expression in E. coli of the B19 capsid protein, it would have been obvious to one of ordinary skill in the art to express the VP1 or VP2 coding sequence in a recombinant host cell for the large scale production of capsid antigen. Furthermore, given the advantages of utilizing the commercially available baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, as well as the previously disclosed use of the baculovirus expression system to produce a vaccine consisting of the canine parvovirus VP2 antigen, it is maintained that it would have been obvious to one of ordinary skill in the art, absent unexpected results, to clone the coding sequence for VP1 or VP2 into a baculovirus expression vector to produce large quantities of authentic capsid antigen.

The declaration of Dr. Spaan, filed 9/29/95, has been considered in maintaining this rejection. Dr. Spaan discusses the individual teachings of the references. However, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Dr. Spaan argues that the prior E. Coli-produced fusion proteins did not contain conformational epitopes, and gave rise to many false negative reactions with human sera. However, at the time the invention was made, it was well known that many bacterially-expressed proteins lacked native conformation. Luckow et al explicitly teaches the ability of baculovirus expression systems to produce proteins closely resembling the native product, including antigenic proteins. Therefore superior results using baculovirus-expressed protein would have been expected. Dr Spaan further argues that Wood et al and Mazzarra et al are not relevant to claims 49-57 because canine parvovirus and human B19 parvovirus are structurally quite dissimilar, citing two publications as evidence. The cited publications were not available at the time the invention was made, and therefore do not illustrate what would have been known to the artisan at the time the invention was made. Dr. Spaan states an opinion that, since there is no antigenic cross-reaction between canine and human parvovirus, the skilled worker would have had no basis to extrapolate on the use of B19 capsid proteins as vaccines or diagnostic agents. However, Ozawa et al (1988) points to several recognized similarities between B19 and other parvoviridae, including location of the capsid proteins on the right side of the genome, and "The dominance of the smaller capsid protein species is a consistent

feature of the parvoviridae, suggesting that the appropriate ratio of capsid proteins is important for the assembly of these viruses". Therefore it is maintained that, despite sequence differences and antigenic differences between the canine and human parvoviruses, those in the parvovirus art would have recognized the canine parvovirus capsid proteins as analogous to B19 parvovirus capsid proteins.

Claims 53, 54, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kajigaya et al or Young et al (5,508,186) in view of French et al and any of Sisk et al, Cotmore et al, Ozawa et al (J. Virol. 61(8):2395-2406), or Ozawa et al (1988). Kajigaya et al and Young et al teach production of B19 virus-like particles containing VP1 and VP2 by expression of the B19 VP1/VP2 open reading frame in CHO cells. The references also teach that the particles can be used in immunofluorescence and ELISA assays. This differs from the claimed invention in that , prior to applicant's effective filing date, the references did not teach a baculovirus expression system. However, French et al teaches production of particles by coexpression of two viral proteins in a baculovirus recombinant, with the particles having the correct, nonequivalent amounts of the two viral proteins. Sisk et al, Cotmore et al, and both Ozawa et al references all teach DNAs encoding the VP1 and the VP2 products. It would have been within the ordinary skill of the art to use a baculovirus expression system to coexpress the VP1 and VP2 coding sequences taught by Sisk et al, Cotmore et al, or Ozawa et al, using a baculovirus coexpression system as taught by French et al for another type of two-component particle, with reasonable expectation of success. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is (703) 308-2926. The examiner can normally be reached on Monday -Thursday and alternate Fridays from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311. A fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196 .

February 12, 1997

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800